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INVESTIGATION OF SERUM BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) LEVELS IN PATIENTS DIAGNOSED WITH SCHIZOPHRENIA WITHOUT ANTIPSYCHOTIC TREATMENT HISTORY

ANTİPSİKOTİK TEDAVİ ÖYKÜSÜ OLMAYAN ŞIZOFRENİ TANILI HASTALARDA SERUMDAKİ BEYİN KAYNAKLI NÖROTROFİK FAKTÖR (BDNF) DÜZEYLERİNİN ARAŞTIRILMASI

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Abstract

BDNF is a member of the neurotrophic family that promotes the development, regeneration, sustaining and maintenance of neuron function in the central nervous system. BDNF modulates neurotransmitter synthesis, metabolism and neuronal activity and is also involved in the development of dopaminergic-related systems, and the mesolimbic dopamine systems. In this study we aimed to investigate the possible differences of serum brain-derived neurotrophic factor (BDNF) levels between the drug-naive patients with schizophrenia and healthy controls. Serum BDNF levels were determined in the serum of 35 drug-naive patients diagnosed as schizophrenia according to SCID-I and DSM-IV-TR criteria and 35 healthy controls subjects matched for gender and age. The schizophrenia symptomatology was assessed by the positive and negative syndrome scale (PANSS). The results showed that BDNF levels were significantly lower in drug-naive patients with schizophrenia than in healthy control subjects (p=0.000). There was a significant difference in BDNF levels between disorganized and paranoid (p = 0.000), disorganized and undifferentiated schizophrenia (p = 0.000) subtypes. There was no significant difference in BDNF levels between the undifferentiated and paranoid schizophrenia subtypes (p = 0.081). The relationship between PANSS scores and subscale scores and serum BDNF levels was not found to be significant (p>0.05). The relationship between general assessment of functionality scores and serum BDNF levels was examined and there was a positive correlation between them (p = 0.07, r = 0.445). Our findings showed decreased BDNF serum levels in a sample of drug-naive patients with schizophrenia. Lower serum levels of BDNF in a sample of drug-naive patients with schizophrenia are consistent with the hypothesis that a deficit in this neurotrophic factor may contribute to the structural and functional alterations of brain underlying in the initial phase of schizophrenia suggesting that neurodevelopmental disturbances may be involved in the pathogenesis of schizophrenia.

Keywords: brain-derived neurotrophic factor; BDNF; schizophrenia

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Özet

Beyin kaynaklı nörotrofik faktör (BDNF) santral sinir sisteminde en geniş dağılımı gösteren nörotrofik faktördür. Santral sinir sistemindeki nöronların gelişimine, rejenerasyonuna ve korunmasına yardımcı olur. Nörotransmitterlerin sentezini, metabolizmasını ve nöronal aktivitesini düzenler; ayrıca dopaminle ilişkili sistemlerin ve mezolimbik dopamin sisteminin gelişimiyle ilişkilidir. Bu çalışmada daha önce tedavi almamış şizofreni hastaları ile sağlam kontrol grubunun serum BDNF düzeyleri arasındaki olası farklılıkların araştırılması amaçlanmıştır. SCID-I ve DSM-IV-TR kriterlerine göre şizofreni tanısı alan daha önce antipsikotik tedavi almamış 35 şizofreni tanılı hasta ile yaş ve cinsiyet olarak eşleştirilmiş 35 kişiden oluşan sağlıklı kontrol grubunun serum BDNF düzeyleri karşılaştırıldı. Şizofreni semptomatolojisi, pozitif ve negatif sendrom ölçeği (PANSS) ile değerlendirildi. Sonuçlar, BDNF düzeylerinin şizofreni hastalarında sağlıklı kontrol deneklerine göre anlamlı olarak daha düşük olduğunu gösterdi (p = 0.000). Dezorganize ve paranoid (p = 0.000), dezorganize ve farklılaşmamış şizofreni (p = 0.000) alt tipleri arasında BDNF düzeylerinde anlamlı bir farklılık vardı. Farklılaşmamış ve paranoid şizofreni alt tipleri arasında BDNF düzeylerinde anlamlı fark yoktu (p = 0.081). PANSS skorları ile alt ölçek puanları ve serum BDNF düzeyleri arasındaki ilişki anlamlı bulunmadı (p> 0.05). Fonksiyonel skorların genel değerlendirmesi ile serum BDNF düzeyleri arasındaki ilişki incelendi ve aralarında pozitif korelasyon bulundu (p = 0.07, r = 0.445). Bulgularımız antipsikotik tedavi almamış şizofreni hastalarının düşük BDNF seviyelerine sahip olduklarını göstermiştir. Antipsikotik ilaç öyküsü olmayan şizofreni hastalarında saptanan düşük BDNF serum düzeyleri, bu nörotrofik faktörle ilgili bir sorunun, şizofreninin başlangıç evresinde yatan beynin yapısal ve fonksiyonel değişikliklerle ilişkisi olabileceği hipotezi ile tutarlıdır.

Anahtar Kelimeler: *beyin kaynaklı nörotrofik faktör; BDNF; şizofreni*

1. Introduction

Schizophrenia; is a mental disorder that manifests symptoms and signs in almost all areas of the mental state, usually beginning in youth, leading to a significant loss of functioning and yet having no complete understanding of etiology. Although the etiology of schizophrenia has been investigated for many years, a proven hypothesis for the cause of the disease has not yet been found. The neurodevelopmental hypothesis is one of these hypotheses (Van & Kapur, 2009; Khan et al., 2013).

An abnormality in the DNA of a patient with schizophrenia can lead to the establishment of false synaptic connections during the prenatal and early childhood brain development and linkage phases. This is due to abnormalities in fetal brain development in the early stages of neuronal selection and migration (Rapaport et al., 2012). Migration begins in the weeks following fertilization and is largely completed by birth. On the other hand, various processes that affect brain structures and synaptogenesis continue throughout life. Potential changes in synaptogenesis may form the basis of learning, emotional maturity, cognitive and motor development throughout life. Periodically and under certain conditions, the neurons deactivate some connections, with apoptosis (programmed cell death) and synaptic pruning (trimming of extended dendrites and thorns) to maintain balance (Woo, 2014; Boksa, 2012). On the other hand, brain-derived neurotrophic factors play a crucial role in the survival of neurons and their ability to function. Neurotrophic factors play important roles in apoptosis programming and execution in the central nervous system. Deficiency due to endogenous or exogenous causes of neurotrophic factors specific to certain neurons is an effect that triggers a chain of biological events that will result in the death of that neuron or group of neurons. Neurons need neurotrophic factors that they secrete for living, differentiating and neuroplasticity (McAllister et al., 1995; Schuman, 1999).

Brain-derived neurotrophic factor (BDNF) is an important member of the neurotrophin family, found in the brain and peripheral tissues. BDNF is a 28-kDa basic dimeric protein consisting of 14-kDa subunits, structurally similar to nerve growth factor (NGF), linked by non-covalent bonds (Rosenthal et al., 1991). BDNF mRNA and proteins have been detected in the hippocampus, amygdala, thalamus, projection fields of the olfactory system, inner and outer pyramidal layers of the neocortex, septum, cerebellum and superior colliculus (Connor & Dragunov, 1998). Although BDNF is present in high concentrations in the nervous system, it is also present in plasma and serum (Radka et al., 1996). Platelets, neurons, and vascular endothelial cells are potential sources of BDNF. The ability of BDNF to cross the blood brain barrier has been shown and based on this it has been reported that serum BDNF levels may reflect the level of BDNF in the brain. The presence of BDNF levels in the human serum suggests that this neurotrophin plays a role in many events, including neuronal regeneration, proliferation of vascular smooth muscle in platelet activation, inflammation and cell proliferation (Shimizu et al., 2003, Pan et al., 1998). The basis of neurodevelopmental theories in schizophrenia etiology is based on neuroimaging studies and neuroimaging studies on young, first episode, non-drug psychotic patients (Bloom, 1993). There are numerous sources of evidence that BDNF levels are altered in schizophrenia brains (Buckley et al., 2007a). Post-mortem studies have shown that BDNF protein levels (measured by ELISA) increase in the cortical areas of patients with schizophrenia and decrease in the hippocampus (Durany et al., 2001). Immunohistochemical studies have shown that schizophrenia increases the expression of BDNF and TrkB-positive neurons in the hippocampus (Iritani et al., 2003), while another study reported increased hippocampal BDNF levels and decreased TrkB levels. Both BDNF and TrkB mRNA levels were found to be significantly lower in prefrontal cortexes (Hashimoto et al., 2005). Although contradictions have been found in these post-mortem studies, all of them point out that schizophrenia BDNF levels have changed (Pillai, 2008). Several studies have shown that BDNF levels in patients with schizophrenia change. There was a decrease in serum BDNF levels in schizophrenia (Tan et al., 2005). In a study by Buckley and colleagues (2007b), the first episode psychosis patients were compared with a normal

healthy control group, and plasma BDNF levels were significantly lower in psychotic patients. The low level of BDNF at the onset of psychosis suggests that BDNF contributes to the pathogenesis of schizophrenia and may be a neurobiological marker to assist in intervention for possible early treatment (Buckley et al., 2007b).

In various studies, the effects of antipsychotic drugs on BDNF levels were assessed using serum or plasma samples from schizophrenia patients and control groups. Serum BDNF levels of schizophrenia patients using clozapine were higher than those using risperidone, but no statistically significant difference was found when compared with patients using typical antipsychotics (Tan et al., 2005). Another study (Hori et al., 2007) reported that eight weeks of olanzapine use did not affect serum BDNF levels prior to olanzapine use. In a study (Rizos et al., 2010), baseline BDNF levels of patients with schizophrenia who did not receive antipsychotic treatment and BDNF levels after six weeks of antipsychotic treatment were compared; it was found that olanzapine-treated patients had a greater increase in serum BDNF levels compared to patients receiving risperidone, haloperidol, and amisulpride. In another study (Xiu et al., 2009), serum BDNF levels of schizophrenia patients using risperidone, clozapine and typical antipsychotics were compared; serum BDNF levels were higher in patients using clozapine and typical antipsychotics compared to those using risperidone. Man et al. (Man et al., 2018) demonstrated that serum BDNF levels in first-episode drug-naïve patients with schizophrenia is significantly low. Heitz et al. (2018) stated that the lower peripheral BDNF levels in at-risk mental state for psychosis compared to first-episode psychosis and chronic schizophrenia might point towards an important drop of this neurotrophin prior to the onset of psychosis. The number of studies involving non-drug users or first-episode schizophrenia patients is increasing. It is thought that it is important to make new studies in terms of providing contribution to the literature and providing data to systematic reviews. In this study, we aimed to compare the BDNF levels of healthy control group with those who did not use any medication for psychotic symptoms before.

2. Material and Methods

2.1. Participants

This is a prospective and analytical case-control study. Between March 2009 and September 2009, patients who were admitted to the Ankara Numune Training and Research Hospital psychiatry clinic (ANTRH) for inpatient or outpatient treatment were taken. According to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR) criteria, diagnosis of schizophrenia was made. Patients were selected from those who did not use drugs before. A total of 35 cases were included in the study. Patients and their relatives accepted to study were informed and approved. Other inclusion criteria were age between 18-55, no physical or organic disease, no menopausal or post-menopausal symptoms, symptoms continued for 6 months or longer. Exclusion criteria were use of other medications (antidepressant, mood stabilizer, thyroid hormone, corticosteroid) for any reason, patients with mental retardation, another Axis-I diagnosis, and substance use. The control group consisted of volunteers age and gender matched to the patients, physically and mentally healthy, and volunteers who did not have schizophrenia or psychotic disorder trait in the first degree relatives.

2.2. Data Collection and Laboratory Analysis

2.2.1. Sociodemographic Data Form

It is a semi-structured form used to identify the sociodemographic characteristics of the cases participating in the study. After the psychiatric interview, the sociodemographic information form was filled. In this form, questions such as age, gender, marital status, educational status, occupation, income level, duration of illness, family history of illness, drug or drug use, smoking are included.

2.2.2. Structured Clinical Interview for DSM-IV Axis-I Disorder (SCID-I)

It is a structured clinical interview scale developed by First et al. (1996) for the establishment of DSM-IV Axis-I diagnoses. The structured interview has been developed to apply the diagnostic evaluation in a standardized manner, to improve the reliability and to systematize it. The validity and reliability study of SCID-I for Turkey was made by Ozkurkcugil et al. (1999).

2.2.3. Positive and Negative Symptom Scale (PANSS)

This scale was developed by Kay et al. (1987) to measure the level, distribution, and severity of positive and negative symptoms of schizophrenia in the subject. The validity and reliability study of the Turkish version of this test was performed by Kostakoglu et al. (1999). The interviewer evaluates the patient. Totally 3 subscales and 30 items. These subscales are positive symptoms, negative symptoms and general psychopathology. The filling of the scale is based on interviews with the patient, observations during interviews, and information from people around the patient (relatives, treatment team, etc.). The rating of each item ranges from 0-7. The subscale total scores are obtained by the sum of subscale items. The total score of the scale is obtained by summing the subscale total scores. The total score ranges from 0-210. The cut-off score was not calculated in the validity and reliability study for the Turkish form of the scale. For this reason, it is used commonly in comparative studies.

2.2.4. Measurement of BDNF Levels

BDNF levels were determined by micro-ELISA method based on sandwich enzyme immunoassay. Quantikine Human BDNF kit was used in the study. Test kit was run in accordance with the principle of kit.

2.2.5. Implementation of Method

All patients were evaluated by the same physician

(OBE). Physical examination of the cases that met the criteria for taking the study was done. An information form containing sociodemographic characteristics has been completed. The PANSS scale was used to assess the clinical status of the cases and the General Assessment of Functionality (GAF) as outlined in Axis-V was performed according to the DSM-IV diagnostic system to assess patients' functionality. Venous blood samples were obtained from antecubital vein of both patient and control group between 8 and 9 a.m. after at least 8 h of starving.

2.3. Statistical Analysis

SPSS for Windows statistical package version 15.0 was used for all statistical analyses. The numerical data were expressed as means and standard deviations, and the categorical data were expressed as frequencies and percentages. The Mann-Whitney test was used to compare the two groups. The Kruskal-Wallis test was used to compare the values of more than one group; the differences between the groups were tested in duplicate using the Tukey's multiple comparison test for significant groups according to the results of this analysis. In addition, Spearman correlation test was used to determine the relationship between variables. The level of significance was taken as 0.05 and the value of "ρ" was compared with the level of significance as calculated in SPSS.

3. Results

Both the patient and control group consisted of 19 (54.3%) women and 16 (45.7%) men. The mean age of the patient group was 37.03 ± 12.70 and the mean age of the control group was 38.65 ± 12.50 (p = 0.540). Other sociodemographic data of the patient and control group are shown in Table 1.

Tablo 1. Sociodemographic Variables of the Patient and Control Group

		Patient N (%) or Mean ± SD	Control N (%) or Mean ±
Gender	Male	16 (45.7%)	16 (45.7%)
	Female	19 (54.3%)	19 (54.3%)
Age (years)		37.03 ± 12.70	38.65 ± 12.52
Marital Status	Married	14 (40.0%)	27 (77.2%)
	Single	17 (48.6%)	4 (11.4%)
	Divorced	4 (11.4%)	4 (11.4%)
Education (years)		9.57 ± 4.80	9.68 ± 4.51
Income Rate	Low (0-1000)	14 (40.0%)	8 (22.8%)
	Moderate (1000-2000)	5 (14.3%)	10 (28.6%)
	Medium-High (2000-3500)	6 (17.1%)	10 (28.6%)
	High (3500 and above)	10 (28.6%)	7 (20.0%)
Number of Siblings		4.23 ± 1.81	3,12 ± 1.25
Psychiatric	First-Degree Relative	11 (31.4%)	0 (0.0%)
History of Family	Distant Relative	9 (25.71%)	0 (0.0%)
Smoking Use		14 (40.0%)	7 (20.0%)

The time from the onset of illness symptoms to the time of admission to the hospital for treatment was questioned. The results are shown in Table 2. The vast majority applied after 5 years (45.7%).

Tablo 2. Time to First Application From the Onset of Disorder-Symptoms

Time-Interval (month)	N	%
6-12	3	8.6
13-24	8	22.9
25-36	4	11.4
37-48	3	8.6
49-60	1	2.9
61 and above	16	45.7
Total	35	100.0

SCID-I was applied to 35 patients who were studied and diagnosed as schizophrenia according to DSM-IV-TR. The schizophrenia subtypes of the cases were identified by SCID-I. According to these results, 17 patients were diagnosed as paranoid schizophrenia, 10 patients were undifferentiated schizophrenia, and 8 patients were diagnosed as disorganized schizophrenia. There were no cases with catatonic and residual schizophrenia subgroups meeting the diagnostic criteria (Table 3).

Tablo 3. Case Distribution According to Schizophrenia Subtypes

Subtype	N (%)	BDNF (ng/ml) ± SD
Paranoid	17 (48.6)	22.44 ± 8.91
Undifferentiated	8 (22.8)	21.18 ± 7.48
Disorganized	10 (28.6)	13.32 ± 5.73

When the mean serum BDNF levels of the patient group and the control group were compared, it was found that there was a significant difference between the two groups (p = 0.000). As a result, mean serum BDNF levels in the patient group were lower than in the control group. In the patient group, there was no significant difference in serum BDNF levels between the sexes (p = 0.660) (Table 4).

Tablo 4. BDNF Levels (ng/ml) of Patient and Control Group

	BDNF Level (ng/ml)		SD	p value	
Patient	17.55 ± 9.48	20.00	8.53	0.660	0.000*
	Male (Mean ± SD)	Total Mean			
	22.90 ± 6.38				
	Female (Mean ± SD)				
Control	43.37	14.67			
Total	31.68	16.74			

**p<0.005*

Notes: *BDNF: Brain-Derived Neurotrophic Factor; SD: Standard Deviation*

Serum BDNF levels of schizophrenia subtypes were calculated. There was a significant difference between mean serum prolactin levels of paranoid, undifferentiated and disorganized schizophrenia subtypes (p = 0.046). There was a significant difference in BDNF levels between disorganized and paranoid (p = 0.000), disorganized and undifferentiated schizophrenia (p = 0.000) subtypes. There was no significant difference in BDNF levels between

the undifferentiated and paranoid schizophrenia subtypes (p = 0.081) (Table 3).

In our study, all patients with schizophrenia were administered PANSS and mean PANSS scores and PANSS subscale scores were calculated. The relationship between PANSS scores and subscale scores and serum BDNF levels was not found to be significant (p = 0.990 for PANSS negative subscale scores, p = 0.546 for PANSS positive subscale scores, p = 0.116 for PANSS general psychopathology sub scores, p = 0.113 for PANSS total scores). The relationship between GAF scores and serum BDNF levels was examined and there was a positive correlation between them (p = 0.07, r = 0.445).

4. Discussion

Neurotrophins are the main proteins responsible for the development, differentiation and migration of cells in the central nervous system during organogenesis and embryogenesis. In adult life these proteins are responsible for regeneration of neurons and regulation of synaptic activity. Thus, neural plasticity in the brain is maintained (Reis et al., 2008). BDNF is the most widely distributed neurotrophic factor in the central nervous system. It helps the development, regeneration and protection of neurons in the central nervous system. It regulates the synthesis, metabolism and neuronal activity of neurotransmitters; as well as the development of dopamine-related systems and the mesolimbic dopamine system (Rizos et al., 2008).

In our study, we compared the serum BDNF levels of schizophrenia patients without antipsychotic use history with the serum BDNF levels of the healthy control group from the neurodevelopmental hypothesis of schizophrenia. As a result of comparison of schizophrenia cases and control group serum BDNF levels, the mean serum BDNF level of schizophrenia group was found to be lower than control group. Findings obtained from our study are consistent with the literature. In the study of Rizos et al. (2008), serum BDNF levels were compared in 14 patients with schizophrenia and 15 healthy controls without antipsychotic treatment. According to the results of this study, the serum BDNF level of the schizophrenia group was statistically significantly lower than the control group. In a study conducted by Chen et al. (2009) serum BDNF levels were compared in 88 patients with schizophrenia who did not receive antipsychotic treatment and 90 control group, and the relationship between schizophrenia subtypes and BDNF was investigated. According to the results of this study, the serum BDNF levels of schizophrenia patients were significantly lower than the control group. In the study of Jindal et al. (2010), Serum BDNF levels of patients diagnosed with schizophrenia were found to be significantly lower than the serum BDNF levels of healthy control group and psychotic patients not diagnosed with schizophrenia. In a study conducted by Pirildar et al. (2004) in our country, the serum BDNF levels of schizophrenia patients were found to be significantly lower than the healthy control group. In recent studies, Man et al. (2018) demonstrated that serum BDNF levels in first-episode drug-naïve patients with schizophrenia is significantly low. In another recent study, Heitz et al. (2018) stated that the lower peripheral BDNF levels in at-risk mental state for psychosis compared to first-episode psychosis and chronic schizophrenia might point towards an important drop of this neurotrophin prior to the onset of psychosis.

There are also studies in the literature comparing the serum BDNF levels of schizophrenia patients receiving antipsychotic treatment with healthy control group. Xiu et al. (2009) found that the serum BDNF levels of schizophrenia patients receiving antipsychotic treatment were significantly lower than the control group. Grillo et al. (2007) compared the serum BDNF levels of schizophrenia patients using clozapine or typical antipsychotic with healthy controls. As a result, they stated that serum BDNF levels of schizophrenia patients in both groups were significantly lower than the control group. There are also studies that find results in the opposite direction. Reis and colleagues (2008) compared serum BDNF levels of schizophrenia patients using antipsychotic with BDNF levels of healthy control group. BDNF levels of schizophrenia patients were significantly higher than the control group. Gama et al. (2007) compared the serum BDNF levels of patients with schizophrenia receiving antipsychotic treatment with healthy control group and euthymic bipolar disorder patients. Serum BDNF levels of schizophrenia patients were found to be significantly higher in both control group and bipolar disorder patients. Patients taking antipsychotics were taken in these studies. In our study, patients who had not used antipsychotic before were taken. These last two studies were also done in Brazil. Genetic differences and the effect of drug use may be the main reason for the differences in the findings of studies.

Chen et al. (2009) found that serum BDNF levels in paranoid schizophrenia patients were significantly higher than other schizophrenia subtypes. In our study, serum BDNF levels of paranoid schizophrenia patients were significantly higher than disorganized schizophrenic patients. Although serum BDNF levels of paranoid schizophrenia patients were higher than those of undifferentiated schizophrenia patients, the difference was not statistically significant. The reason for this may be the inadequate number of patients in our study. Huang and Lee (2006) found that serum BDNF levels of catatonic schizophrenia patients were significantly lower than those of residual and paranoid schizophrenia patients. These results suggest that the subtypes of schizophrenia may be source from different biological bases. However, there is a need for more research to be able to put this out more precisely.

Studies in which the relationship between serum BDNF levels and PANSS scores were investigated in the literature revealed different results. Chen et al. (2009) found a positive correlation between PANSS positive subscale scores and BDNF, but not between PANSS negative subscale scores and BDNF. Rizos et al. (2008) found a negative correlation between both positive and negative subscale scores and serum BDNF levels. Reis et al. (2008) found no positive correlation between serum BDNF level and PANSS positive subscale scores, but found a positive correlation between PANSS negative subscale scores and BDNF. Huang and Lee (2006) found

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a significant relationship between serum BDNF and PANSS subscale scores consistent with our results. The reasons for these differences that arise in studies are not known precisely. However, these differences may be due to differences in the clinical status of the patients, the duration of the disease, or the frequency of alleles due to BDNF gene polymorphism (Chen et al., 2009). GAF scores of schizophrenia patients were compared with serum BDNF levels and positive correlations were found between them. When serum BDNF levels of schizophrenia patients were lowered, GAF scores were also found to decrease. A positive correlation between GAF scores and BDNF may reflect a relationship between BDNF and disease severity.

The most important limitation of our study is that our sample size is low. We also do not know how long the stress level affects the BDNF measurement. It has been shown that different stress sources may reduce BDNF levels during studies. The stress they experience due to the symptoms of schizophrenia patients may be affecting BDNF levels (Smith et al., 1995). In conclusion, our findings show that schizophrenia patients without antipsychotic treatment have low BDNF levels. This may be a reflection of the impaired neurodevelopmental process in schizophrenia patients. Enlightening the role of BDNF in schizophrenia can help to develop new therapeutic strategies in the treatment of schizophrenia. In order to better understand the role of BDNF in schizophrenia, we need to conduct research on larger groups of patients.

Competing interests

The authors declare that they have no competing interest.

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